UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Toxicology Data Submitted for Copper Naphthenate, 8% Active Ingredient.

EPA Identification Numbers:
DP Barcode: D216160
Submission: S488351
P.C. Code: 023102
MRID #'s 43643701 through 43643704

TO: Mark Wilhite / Yvonne Brown
Product Manager # 51
Special Review and Reregistration Division (7508W)

FROM: Timothy F. McMahon, Ph.D. 5/22/96
Pharmacologist, Review Section I
Toxicology Branch II, Health Effects Division (7509C)

THRU: Yiannakis M. Ioannou, Ph.D. Y.M. Ioannou 5/22/96
Section Head, Review Section I
Toxicology Branch II, Health Effects Division (7509C)

and

Stephanie R. Irene, Ph.D.
Acting Chief, Toxicology Branch II
Health Effects Division (7509C)
Stephanie R. Irene 5/23/96

Registrant: Dussek Campbell Limited

Action Requested: Review of acute toxicity studies submitted for copper naphthenate, 8% active ingredient.

Executive Summaries

1) CITATION: Kuhn, J.O.(1992): Acute Oral Toxicity Study in Rats. StillMeadow, Inc. Laboratory Study No. 9542-92. MRID # 43643701. Unpublished.

In an acute oral toxicity study (MRID # 43643701), groups of 5 male and female fasted young adult Sprague-Dawley rats were given a single oral dose of 8% copper naphthenate (no vehicle, test article administered as supplied) at doses of 450, 2000, 4000, and 5050 mg/kg and observed for 14 days post-treatment.

Oral LD_{50} in Males = >5050 mg/kg
Oral LD_{50} in Females = > 5050 mg/kg
Combined Oral LD_{50} = > 5050 mg/kg

Copper naphthenate 8% a.i. is TOXICITY CATEGORY IV.

This acute oral toxicity study is classified **acceptable** and satisfies the guideline requirement for an acute oral toxicity study in rats.

2) CITATION: Kuhn, J.O.(1992): Acute Dermal Toxicity Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9543-92. MRID # 43643702. Unpublished.

In an acute dermal toxicity study (MRID # 43643702), 5 male and 5 female young adult New Zealand White rabbits were dermally exposed to 2020 mg/kg copper naphthenate for 24 hours to 10% of the total body surface area. Rabbits were then observed at 0.5, 3.0, and 6.0 hours post-treatment and daily thereafter for 14 days post-dose. Gross necropsy was performed at the end of the study.

Dermal LD_{50} in Males = >2020 mg/kg
Dermal LD_{50} in Females = > 2020 mg/kg
Combined Dermal LD_{50} = > 2020 mg/kg

Copper naphthenate 8% a.i. is TOXICITY CATEGORY III.

This acute dermal toxicity study is classified **acceptable** and satisfies the guideline requirement for an acute dermal toxicity study in rabbits.

3) CITATION: Kuhn, J.O.(1992): Primary Eye Irritation Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9544-92. MRID # 43643703. Unpublished.

In a primary eye irriation study (MRID # 43643703), 0.1ml of 8% copper naphthenate was instilled in to the conjunctival sac of 9 young adult New Zealand White rabbits. Six of the rabbits (three male and three female) were exposed for 24 hours in the right eye. Three of the animals (three males) were washed with room temperature water for one minute beginning 30 seconds after treatment. Treated eyes were examined at 1, 24, 48, and 72 hours after treatment. Irritation was scored according to the scale presented in the report. Conjunctival irritation (redness) was observed in all rabbits at 1 hour and 24 hours post-dose, and in one rabbit at 48 hours post-dose. Chemosis was observed in one washed rabbit eye at 24 hours post-dose. There were no other ocular effects reported in this study. In this study, 8% copper napthenate is a minimal eye irritant and is TOXICITY CATEGORY III.

This study is classified as **acceptable** and satisfies the guideline requirement for a primary eye irritation study (81-4) in rabbits.

4) CITATION: Kuhn, J.O.(1992): Primary Dermal Irritation Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9545-92. MRID # 43643704. Unpublished.

In a primary dermal irriation study (MRID # 43643704), 0.5ml of undiluted 8% copper naphthenate was applied to intact skin sites of 6 young adult New Zealand White rabbits. Exposure was for 4 hours. After removal of dressings, observations for dermal irritation were made at 0.75, 24, 48, and 72 hours post-dose, and then on days 7, 10, 14, 17, and 21 post-treatment. Very slight to well-defined erythema/eschar and very slight to slight edema was observed up to 17 days post-washing. The primary irritation index was 1.1, and was used to describe 8% copper naphthenate as slightly irritating. Based on the 72 hour observations of dermal reaction, a Toxicity Category of III was assigned.

This study is classified as **acceptable** and satisfies the guideline requirement for a primary dermal irritation study (81-5) in rabbits.

EPA Reviewer: [signature] Date 5/22/96
Review Section I, Toxicology Branch II
EPA Secondary Reviewer: [signature] Date 5/22/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat
OPPTS 870.1100 (§81-1)

DP BARCODE: D216160
P.C. CODE: 023102

SUBMISSION: S488351
TOX. CHEM. No: 245

TEST MATERIAL: Copper Naphthenate, 8% a.i.

SYNONYMS: none stated

CITATION: Kuhn, J.O.(1992): Acute Oral Toxicity Study in Rats. StillMeadow, Inc. Laboratory Study No. 9542-92. MRID # 43643701. Unpublished.

SPONSOR: Dussek Campbell Limited, Belleville, Ontario

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 43643701), groups of 5 male and female fasted young adult Sprague-Dawley rats were given a single oral dose of 8% copper naphthenate (no vehicle, test article administered as supplied) at doses of 450, 2000, 4000, and 5050 mg/kg and observed for 14 days post-treatment.

Oral LD_{50} in Males = >5050 mg/kg
Oral LD_{50} in Females = > 5050 mg/kg
Combined Oral LD_{50} = > 5050 mg/kg

Copper naphthenate 8% a.i. is TOXICITY CATEGORY IV.

This acute oral toxicity study is classified **acceptable** and satisfies the guideline requirement for an acute oral toxicity study in rats.

COMPLIANCE: Signed and dated statements of GLP, No Data Confidentiality, and Quality Assurance were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Copper Naphthenate, 8% a.i.
   Description: clear dark green liquid
   Product Code: A00101
   Purity: 8% (label claim)
   CAS # 1338-02-9

2. Vehicle and/or positive control: not applicable

3. Test Animals: Species: Rat
   Strain: HSD:(SD)
   Weight when tested: males, 186-290g; females, 178-215g.
   Source: Harlan Sprague-Dawley, Inc., Houston, Texas
   Acclimation period: at least five days

   Diet: Purina Formulab Chow #5008, *ad libitum*
   Water: tap water, *ad libitum*
   Housing: singly, in suspended, wire bottom, stainless steel cages.

   Environmental conditions: not stated

B. STUDY DESIGN AND METHODS:

1. In -life dates - start: 11/4/92 end: 12/9/92

2. Animal assignment and treatment: Healthy rats were released from quarantine, and five males and five females per dose level were selected. Following a 16 hour fast prior to treatment, rats were given a single oral dose of undiluted test material and returned to their cages. Observations for mortality and signs of toxicity were made at least three times on the day of treatment and at least once daily thereafter for 14 days. Individual body weights were recorded just prior to treatment and on days 7 and 14. A gross necropsy was conducted on each rat at study termination. The following table summarizes the study design (Table 1):

TABLE 1

Dose (mg/kg)	Dose (ml/kg)	Mortality Males	Mortality Females	Mortality Combined
450	0.444	0/5	0/5	0/10
2000	1.97	0/5	0/5	0/10
4000	3.95	0/5	0/5	0/10
5050	4.98	0/5	0/5	0/10

data taken from page 9 of the report.

II. RESULTS AND DISCUSSION

A. Mortality

The above table shows that at all doses tested in this study, there was no mortality in either male or female rats.

B. Clinical Observations

According to the report, prominent clinical signs during the study included diarrhea, discolored feces and piloerection at the 5050 mg/kg dose level. In males, green feces was observed in 3 of 5 rats at 6 hours post-dose but not thereafter. In female rats, diarrhea was observed in one rat at 6 hours post-dose and again on day 5 post dose, but not thereafter. Piloerection was observed in one female rat on day 5 post-dose but not thereafter.

C. Body Weight

Two male rats at the 5050 mg/kg dose level lost weight during days 0-7 of the study (11 gram loss and 15 gram loss respectively), and one female rat at the 450 mg/kg dose level lost weight during days 7-14 of the study (1 gram loss).

D. Necropsy

There were no treatment related abnormalities observed at gross necropsy in any of the rats.

The oral LD_{50} for male and female rats in this study is > 5050 mg/kg.

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EPA Reviewer: _____ Date 5/22/96
Review Section I, Toxicology Branch II
EPA Secondary Reviewer: _____ Date 5/22/96

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rabbit
OPPTS 870.1200 (§81-2)

DP BARCODE: D216160
P.C. CODE: 023102

SUBMISSION: S488351
TOX. CHEM. No: 245

TEST MATERIAL: Copper Naphthenate, 8% a.i.

SYNONYMS: none stated

CITATION: Kuhn, J.O.(1992): Acute Dermal Toxicity Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9543-92. MRID # 43643702. Unpublished.

SPONSOR: Dussek Campbell Limited, Belleville, Ontario

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 43643702), 5 male and 5 female young adult New Zealand White rabbits were dermally exposed to 2020 mg/kg copper naphthenate for 24 hours to 10% of the total body surface area. Rabbits were then observed at 0.5, 3.0, and 6.0 hours post-treatment and daily thereafter for 14 days post-dose. Gross necropsy was performed at the end of the study.

Dermal LD_{50} in Males = >2020 mg/kg
Dermal LD_{50} in Females = > 2020 mg/kg
Combined Dermal LD_{50} = > 2020 mg/kg

Copper naphthenate 8% a.i. is TOXICITY CATEGORY III.

This acute dermal toxicity study is classified **acceptable** and satisfies the guideline requirement for an acute dermal toxicity study in rabbits.

COMPLIANCE: Signed and dated statements of GLP, No Data Confidentiality, and Quality Assurance were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Copper Naphthenate, 8% a.i.
   Description: clear dark green liquid
   Product Code: A00101
   Purity: 8% (label claim)
   CAS # 1338-02-9

2. Vehicle and/or positive control: not applicable

3. Test Animals: Species: Rabbit
   Strain: New Zealand White
   Weight when tested: males, 2.15-2.90kg; females, 2.2-2.825kg.
   Source: Ray Nichols Rabbitry, Lumberton, Texas
   Acclimation period: at least five days

   Diet: Purina Rabbit Chow, presented in measured amounts
   Water: tap water, *ad libitum*
   Housing: singly, in suspended, wire bottom, stainless steel cages.

   Environmental conditions: not stated

B. STUDY DESIGN AND METHODS:

1. In -life dates - start: 10/29/92 end: 11/12/92

2. Animal assignment and treatment: Healthy rabbits were released from quarantine, and the rabbits prepared for treatment on the day prior to test article application by clipping the dorsal surface of the trunk free of hair. Not less than 10% of total body surface was exposed. Only those rabbits with exposure areas free of pre-existing skin irritation or defects were used for this study. All rabbits selected for use were treated with 2020 mg/kg (1.99 ml/kg) of undiluted test material. Test material was evenly applied and held in contact with the skin by using surgical gauze. Non-irritating adhesive tape was used to hold the gauze in place. The entire trunk was then wrapped with a semi-permeable dressing to retard evaporation of volatile substances and to prevent possible ingestion of test material. Wrappings were secured in place with non-irritating adhesive tape.

After 24 hours of exposure, the wrappings and gauze were removed. Exposed areas were gently washed with room temperature tap water and a clean wet cloth to remove as much remaining test material as possible. Rabbits were returned to their cages after washing. At study termination, a gross necropsy was conducted.

II. RESULTS AND DISCUSSION

A. Mortality

There was no mortality in either male or female rabbits.

B. Clinical Observations

There were no clinical signs of toxicity in male or female rabbits.

C. Body Weight

There were no significant effects on body weight in male and female rabbits.

D. Necropsy

There were no treatment related abnormalities observed at gross necropsy in any of the rabbits.

The dermal LD_{50} for male and female rabbits in this study is > 2020 mg/kg.

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EPA Reviewer: _____ Date 5/22/96
Review Section I, Toxicology Branch II
EPA Secondary Reviewer: _____ Date 5/22/96

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit
OPPTS 870.2400 (§81-4)

DP BARCODE: D216160
P.C. CODE: 023102

SUBMISSION: S488351
TOX. CHEM. No: 245

TEST MATERIAL: Copper Naphthenate, 8% a.i.

SYNONYMS: none stated

CITATION: Kuhn, J.O.(1992): Primary Eye Irritation Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9544-92. MRID # 43643703. Unpublished.

SPONSOR: Dussek Campbell Limited, Belleville, Ontario

EXECUTIVE SUMMARY: In a primary eye irriation study (MRID # 43643703), 0.1ml of 8% copper naphthenate was instilled in to the conjunctival sac of 9 young adult New Zealand White rabbits. Six of the rabbits (three male and three female) were exposed for 24 hours in the right eye. Three of the animals (three males) were washed with room temperature water for one minute beginning 30 seconds after treatment. Treated eyes were examined at 1, 24, 48, and 72 hours after treatment. Irritation was scored according to the scale presented in the report. Conjunctival irritation (redness) was observed in all rabbits at 1 hour and 24 hours post-dose, and in one rabbit at 48 hours post-dose. Chemosis was observed in one washed rabbit eye at 24 hours post-dose. There were no other ocular effects reported in this study. In this study, 8% copper napthenate is a minimal eye irritant and is TOXICITY CATEGORY III.

This study is classified as **acceptable** and satisfies the guideline requirement for a primary eye irritation study (81-4) in rabbits.

COMPLIANCE: Signed and dated statements of GLP, No Data Confidentiality, and Quality Assurance were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Copper Naphthenate, 8% a.i.
   Description: clear dark green liquid
   Product Code: A00101
   Purity: 8% (label claim)
   CAS # 1338-02-9

2. Vehicle and/or positive control: not applicable

3. Test Animals: Species: Rabbit
   Strain: New Zealand White
   Weight when tested: not applicable
   Source: Ray Nichols Rabbitry, Lumberton, Texas
   Acclimation period: at least five days

   Diet: Purina Rabbit Chow, presented in measured amounts
   Water: tap water, *ad libitum*
   Housing: singly, in suspended, wire bottom, stainless steel cages.

   Environmental conditions: not stated

B. STUDY DESIGN AND METHODS:

1. In -life dates - start: 10/26/92 end: 10/29/92

2. Animal assignment and treatment: Both eyes of each rabbit used in this study were carefully examined at least 24 hours prior to treatment with a fluorescein sodium ophthalmic solution. Both eyes were again examined just prior to treatment, but without the opththalmic solution. Only those rabbits without eye defects or irritation were selected for testing.

Rabbits were held firmly until quiet. A dose of 0.1 ml of the undiluted test material was placed into the conjunctival sac of the right eye of each rabbit by gently rolling the lower lid away from the eyeball to form a cup into which the test material was dropped. Lids were gently held together for one second. Three of the treated eyes were each washed with room temperature deionized water for one minute beginning 30 seconds after treatment. The

corneas of all treated eyes were examined immediately after the 24 hour observation with fluorescein sodium ophthalmic solution. Any corneas exhibiting positive staining were re-examined with the ophthalmic solution at each successive observation time until fluorescein staining no longer occurred. All treated eyes were washed with room temperature deionized water for one minute immediately after recording the 24 hour observation.

Individual irritation scores for each rabbit at each scheduled observation were determined using a grading scale as presented in the report. An average irritation score for each scheduled observation for all nonwashed and washed eyes was then determined, based on the number of animals tested in those groups. A maximum average irritation score for nonwashed and washed eyes was derived from the observation yielding the highest average irritation score. The maximum average irritation scores were used to rate the test material according to the ratings presented in the report.

II. **RESULTS AND DISCUSSION**

Ocular reactions to treatment were presented for the individual rabbits on pages 17-19 of the report. The maximum average scores for unwashed and washed eyes were presented on page 20 of the report. For those rabbits in the unwashed group, all six rabbits were observed to have redness of the conjunctiva at 1 hour post-treatment with a score of "2" (defined as "diffuse, crimson color, individual vessels not easily discernable"). At 24 hours post-treatment, the three male rabbits were found to have redness scores of "1" (some blood vessels definitely hyperemic), while the three females were still scored as "2" for this lesion. There were no reactions observed at subsequent observation times in this group.

In the group whose eyes were washed after treatment, all three rabbits were scored with redness of the conjuntiva at 1 hour post dose, with a score of "2." This degree of irritation persisted at 24 hours for all three rabbits. By 48 hours, only one of the three rabbits was scored with conjunctival redness, and this rabbit had a score of "1."

The maximum average score for nonwashed rabbit eyes was 4.7 at 1 hour and 3.0 at 24 hours post-dose. The maximum average score for washed rabbit eyes was 4.0 at 1 hour, 4.7 at 24 hours, and 0.7 at 48 hours post-dose. The maximum average score of 4.7, observed in both the washed and unwashed eyes, was used to rate 8% copper naphthenate as minimally irritating.

EPA Reviewer: [signature] Date 5/22/96
Review Section I, Toxicology Branch II
EPA Secondary Reviewer: [signature] Date 5/22/96

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS 870.2500 (§81-5)

DP BARCODE: D216160
P.C. CODE: 023102

SUBMISSION: S488351
TOX. CHEM. No: 245

TEST MATERIAL: Copper Naphthenate, 8% a.i.

SYNONYMS: none stated

CITATION: Kuhn, J.O.(1992): Primary Dermal Irritation Study in Rabbits. StillMeadow, Inc. Laboratory Study No. 9545-92. MRID # 43643704. Unpublished.

SPONSOR: Dussek Campbell Limited, Belleville, Ontario

EXECUTIVE SUMMARY: In a primary dermal irriation study (MRID # 43643704), 0.5ml of undiluted 8% copper naphthenate was applied to intact skin sites of 6 young adult New Zealand White rabbits. Exposure was for 4 hours. After removal of dressings, observations for dermal irritation were made at 0.75, 24, 48, and 72 hours post-dose, and then on days 7, 10, 14, 17, and 21 post-treatment. Very slight to well-defined erythema/eschar and very slight to slight edema was observed up to 17 days post-washing. The primary irritation index was 1.1, and was used to describe 8% copper naphthenate as slightly irritating. Based on the 72 hour observations of dermal reaction, a Toxicity Category of III was assigned.

This study is classified as **acceptable** and satisfies the guideline requirement for a primary dermal irritation study (81-5) in rabbits.

COMPLIANCE: Signed and dated statements of GLP, No Data Confidentiality, and Quality Assurance were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Copper Naphthenate, 8% a.i.
   Description: clear dark green liquid
   Product Code: A00101
   Purity: 8% (label claim)
   CAS # 1338-02-9

2. Vehicle and/or positive control: not applicable

3. Test Animals: Species: Rabbit
   Strain: New Zealand White
   Weight when tested: not applicable
   Source: Ray Nichols Rabbitry, Lumberton, Texas
   Acclimation period: at least five days

   Diet: Purina Rabbit Chow, presented in measured amounts
   Water: tap water, *ad libitum*
   Housing: singly, in suspended, wire bottom, stainless steel cages.

   Environmental conditions: not stated

B. STUDY DESIGN AND METHODS:

1. In -life dates - start: 10/27/92 end: 11/17/92

2. Animal assignment and treatment: Healthy rabbits were released from quarantine. The day prior to treatment, each rabbit was prepared by clipping the dorsal area of the trunk free of hair to expose an area at least 8 x 8 cm. Each exposure area was large enough to include both a test site and a control area. Only those animals with exposure areas free of pre-existing skin irritation or defects were selected for testing. Each test site was treated with 0.5 ml of undiluted test material by introducing the test material beneath a surigcal gauze patch measuring 2.5 x 2.5 cm and two single layers thick. Each patch was secured in place with a strip of non-irritating adhesive tape. The entire trunk of each animal was loosely wrapped with a semi-permeable dressing to retard evaporation of volatile substances and to prevent possible ingestion of the test material. The wrappings were held in place with non-irritating tape.

Four hours after treatment, the wrappings and patches were removed. Test sites were gently washed with room temperature tap water and a wet cloth to remove as much residual test material as possible. The test sites were observed for erythema and eschar formation, edema, or any other dermal defects or irritation. Observation times were 0.75, 24, 48, and 72 hours after washing, and on days 7, 10, 14, 17, and 21 after washing.

For each animal, all of the erythema and edema scores were added through 72 hours, and the sum was divided by 4 to obtain an individual irritation score. The primary irritation index was determined by calculating the mean of the irritation scores for the six animals and was used to obtain a rating for the test material according to the scale presented in the report. A Toxicity Category was assigned based only on the observations at 72 hours.

II. RESULTS AND DISCUSSION

Dermal irritation reactions were shown on page 13 of the report for all six rabbits used in this study. At 48 and 72 hours after washing as well as on day 7, well defined erythema/eschar was observed in 2 of 6 rabbits, while very slight erythema/eschar was observed in the remaining 4 rabbits. Erythema/eschar formation was observed up to 17 days post-washing in 4 of the 6 rabbits (grade of "1"; very slight).

At 48 hours post-washing, very slight edema was observed in 3 of 6 rabbits. By 72 hours post-washing, 3 of 6 were observed with very slight edema, while the remaining three had slight edema. Edema was observed up to day 17 post-washing, where 3 rabbits were observed with very slight edema.

A Primary Irritation Index of 1.1 was obtained for this study, and was used to describe 8% copper naphthenate as slightly irritating. Based on the 72 hour observations, a Toxicity Category of III was obtained.